CLINICAL STUDY

Resting Heart Rate and Metabolic Syndrome in Patients With Diabetes and Coronary Artery Disease in Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

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The relation between the metabolic syndrome (MetS) and resting heart rate (rHR) in patients with diabetes and coronary artery disease is unknown. The authors examined the cross-sectional association at baseline between components of the MetS and rHR and between rHR and left ventricular ejection fraction in the population from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) randomized clinical trial. The mean rHR in the MetS group was significantly higher than in those without (68.4±12.3 vs 65.6±11.8 beats per min, P=.0017). The rHR was higher (P<.001 for trend) with increasing number of components for MetS. Linear regression analyses demonstrated that as compared to individuals without MetS, rHR was significantly higher in participants with MetS (regression coefficient, 2.9; P=.0015). *In patients with type 2 diabetes and coronary artery disease, the presence of higher rHR is associated with increasing number of criteria of MetS and the presence of ventricular dysfunction.* **Prev Cardiol. 2010;13:112–116.** ©2010 *Wiley Periodicals, Inc.*

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The importance of resting heart rate (rHR) as a prognostic factor and potential therapeutic target is not yet generally accepted.[1] A large number of studies have shown that high rHR is a predictor of increased morbidity and mortality among people with coronary artery disease (CAD)[1–3] and diabetes.[4] Higher rHR is also associated with incident diabetes.[5]

Heart rate has shown to be related to insulin sensitivity and insulin secretion,[6] while elevated heart rate has been shown to precede the development of the metabolic syndrome (MetS).[7] MetS is associated with autonomic dysfunction[8]; thus, elevated rHR may be a marker of absolute or relative sympathetic overactivity.

A recent meta-analysis showed that MetS is associated with increased risk of cardiovascular events and death.[9] Another study showed that high rHR clusters with other cardiovascular risk factors, such as hypertension, diabetes, and hypertriglyceridemia.[10] However, the relation between MetS and rHR in patients with diabetes and CAD is unknown, and there remains a need to identify interventions targeting rHR or the mechanisms behind it.

Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) is a National Institutes of Health–sponsored randomized clinical trial evaluating treatment for patients with type 2 diabetes and angiographically documented stable CAD.[11]

We examined the association between components of the MetS and rHR in this patient population at baseline. We also evaluated the relationship between rHR and left ventricular ejection fraction (LVEF).

METHODS

The study design, including specific inclusion and exclusion criteria for BARI 2D participants, is summarized elsewhere.[11] MetS was defined by the criteria of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III).[12] Since all patients had type 2 diabetes, MetS was defined as presence of ≥ 2 of the following components: (1) waist circumference >102 cm in men and >88 cm in women; (2) triglycerides ≥ 150 mg/dL; (3) high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women; and (4) blood pressure $\geq 130/\geq 85$ mm Hg or being treated for hypertension.

Heart rate was evaluated from standard 12-lead resting electrocardiography recorded with the patient supine and resting. Analyses were performed according to the Minnesota code.[13] We excluded all patients with history of atrial fibrillation. All electrocardiographic results were evaluated by an experienced cardiologist who was masked to the diagnosis and outcome of the individual patients. LVEF was measured (n=2117) at each of the clinical sites with the modality of choice of that site. The modes were angiography (69%), perfusion scanning (20%), transthoracic echocardiography (6%), and other (4%).

Baseline characteristics were compared across heart rate quartiles using chi-square tests of general association for proportions. Continuous data were compared across heart rate quartiles using analysis of variance F-tests if normally distributed and the Kruskal-Wallis test if the data were non-normal. Linear trends in proportions of the baseline characteristics across heart rate quartiles were tested using the Cochran-Mantel-Haenszel chi-square. Unadjusted linear models of rHR were used to obtain estimates of average change in rHR due to higher number of MetS components. Increasing trends in rHR by number of MetS risk factors were detected by adding linear contrasts to each of the unadjusted regression models. Adjusted models including age, sex, ethnicity, β-blocker use, calcium channel blocker use, exercise, smoking status, and prior revascularization were used to determine the independent relationship of MetS with rHR. Similar unadjusted and adjusted linear models were also used to determine the relationship between rHR and LVEF.

In order to determine which MetS component accounted for the most variability in rHR, a reference model of rHR that included age, sex, ethnicity, β-blocker use, calcium channel blocker use, exercise, smoking status, and prior revascularization was first constructed and the R^2 noted. Then 4 separate models were constructed, each including all the covariates from the reference model and one of the components of MetS. The difference between the R^2 of the reference model and the R^2 from each of the component models was calculated. These 4 differences were then compared to determine which MetS component explained the most variability in rHR.

RESULTS

We evaluated 2214 BARI 2D participants with complete baseline records including measurement of the rHR. The mean rHR was 68.2 (range, 36–110) beats per min (bpm). The participants in the increasing rHR quartile had significantly ($P<.001$ for trend) greater body mass index and higher hemoglobin A_{1c} (HbA_{1c}) value and were more likely to be female and smokers (Table I).

In BARI 2D, of the 2174 participants who had all the variables required for MetS criteria, 92.4% met the described definition of MetS at baseline. The mean rHR in the MetS group was significantly higher than in those without (68.4 ± 12.3 vs 65.6 ± 11.8 bpm, $P=.0017$). Adjusted linear regression analyses demonstrated that as compared to individuals without MetS, rHR was significantly higher in participants with MetS (regression coefficient, 2.9; $P=.0015$). The rHR was higher ($P<.001$ for trend) with increasing number of components for MetS. This trend was also observed in an adjusted linear model (Table IIB). Table IIC shows the amount of variation of rHR explained by each of the individual components of MetS. The reference model for rHR included age, sex, ethnicity, smoking status, and prior revascularization status and had an R^2 of 0.0279; after addition of waist circumference, the R^2 increased to 0.0413. Based on the change in R^2 from each of the 4 MetS component models to the reference model, waist circumference explained the most variation in rHR. The coefficient from the regression model for waist circumference category was 3.5. In the adjusted model, HbA1c accounted for about 1.8% of the variability in heart rate.

Table III shows that the rHR was significantly higher in participants with lower LVEF categories ($P=.007$ for trend). Compared to participants with LVEFs of $\geq 55\%$, participants with LVEFs <35% had adjusted regression coefficient of 4.3 ($P<.001$) (Table IIIB). We also observed that 1.1% of the variation in heart rate was explained by the MetS factors after accounting for LVEF.

DISCUSSION

In this cross-sectional analysis, we demonstrate that in patients with type 2 diabetes and confirmed CAD, the presence of MetS is associated with higher rHR, with waist circumference contributing the most to this relationship. We also showed that there was a graded increase in rHR with decreasing LVEF.

A recent study[14] has shown that heart rate variability (HRV) indices in the group with MetS were

Table I. Baseline Characteristics of Patients Stratified by Heart Rate

	Total (N=2214)	HR <60 bpm (N=581)	HR 60–67 bpm (N=535)	HR 68–75 bpm (N=552)	HR >75 bpm (N=546),	P Value
Age at study entry, y (mean, SD)	62.3, 8.9	63.4, 8.6	62.4, 8.9	61.9, 8.5	61.2, 9.4	.0014
Female	29.8%	24.3%	29.9%	30.4%	35.0%	.0003
Ethnicity						
Black nH	16.8%	14.8%	15.7%	15.9%	20.7%	.04
Hispanic	13.0%	14.8%	10.8%	12.1%	14.1%	
White nH	65.4%	64.2%	68.2%	68.1%	61.4%	
Asian/other nH	4.8%	6.2%	5.2%	3.8%	3.8%	
Exercise regularly	25.6%	28.4%	25.1%	21.0%	27.9%	.018
Current smoker	12.5%	9.5%	10.7%	15.0%	15.0%	.005
BMI, kg/m^2 (mean, SD)	31.7, 5.9	31.1, 5.6	31.2, 5.7	31.9, 5.7	32.7, 6.4	<.001
Waist circumference (>102 cm men, >88 cm women)	74.2%	68.2%	79.4%	76.9%	82.4%	<.001
Lipid values, mg/dL (mean, SD)						
Total cholesterol	169.6, 40.5	165.1, 38.0	167.5, 38.3	169.8, 39.3	166.5, 45.4	<.001
LDL cholesterol	96.5, 33.2	94.6, 31.5	95.1, 32.5	96.1. 34,1	100.5, 34.6	.017
HDL cholesterol	38.3, 10.3	38.2, 13.8	38.4, 10.2	38.2, 10.7	38.3, 10.4	<.99
Triglycerides (mean, median)	179.8, 149	163.1, 139	176.1, 147	186.0, 158	194.9, 155	.007
Blood pressure, mm Hg (mean, SD)						
Systolic	131.8, 20.1	132.8, 21.2	131.6, 19.8	132.0, 20.3	130.7, 19.2	.35
Diastolic	74.7, 11.2	73.9, 11.1	74.5, 11.2	74.5, 10.9	75.8, 11.7	.026
History of treated hypertension, %	82.5	82.9	82.0	83.1	81.9	.94
Hemoglobin A$_{1c}$, % (mean, SD)	7.67, 1.61	7.36, 1.53	7.58, 1.53	7.76, 1.57	8.02, 1.75	<.001
Diabetes duration, y (mean, SD)	10.4, 8.6	9.7, 8.7	10.4, 8.5	10.7, 8.4	10.7, 8.9	.14
Insulin use	27.9%	20.7%	25.2%	32.4%	33.5%	<.001
β-Blocker use	73.1%	83.1%	80.4%	69.1%	59.4%	<.001
Prior CABG	6.1%	5.9%	7.9%	5.1%	5.9%	.26
Prior PCI	19.8%	21.3%	21.5%	18.8%	17.4%	.25

Abbreviations: BMI, body mass index; bpm, beats per min; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; nH, non-Hispanic; PCI, percutaneous coronary intervention; SD, standard deviation.

significantly lower than those in the group without MetS (P<.05). Furthermore, a significant negative correlation was found between all components of MetS and the HRV indices; additionally, as the number of MetS components increased, the HRV indices gradually decreased. Data regarding the relationship between heart rate and MetS are, however, lacking. Ioune and associates[10] showed that the odds of having increased heart rate (>77 bpm) increased with increasing number of risk factors such as hypertension, diabetes mellitus, and hypertriglyceridemia.

Increased heart rate is a marker of lower parasympathetic tone or higher sympathetic activity,[15] and higher sympathetic tone can cause insulin resistance by adrenergic stimulation.[16] Conversely, insulin resistance and hyperinsulinemia can cause sympathetic overactivity, leading to cardiac autonomic dysfunction.[17,18] In our study, patients with more MetS risk factors had higher rHR, and such risk factors have been hypothesized to be also related to sympathetic overactivity.[8,19,20] A recent study showed that sympathetic nerve traffic was significantly greater in persons with MetS than in controls.[21] Increased heart rate due to an autonomic dysfunction with absolute or relative sympathetic overactivity may be one way MetS imparts higher risk for cardiovascular disease.

We showed that out of all the components of MetS, waist circumference was most correlated to rHR. A recent study[22] showed that waist circumference was a better correlate of HRV parameters than body mass index and that obesity was related to sympathovagal imbalance characterized by depressed parasympathetic tone and increased sympathetic activity. Moreover, several associations between HRV parameters and adipokines were observed, indicating a possible link between adipokines and disturbances of the autonomic nervous system.

We also showed that higher rHR was associated with worsening left ventricular dysfunction. It has been reported that in patients with ischemic heart

Table II. Relationship of Metabolic Syndrome (MetS) and Presence of Number and Type of Its Components and Heart Rate

A. TOTAL FOR METS ANALYSES (N=2174)	HEART RATE, MEAN±SD	P VALUE	UNIVARIATE REGRESSION COEFFICIENT (Y/N)	P VALUE	ADJUSTED[a] REGRESSION COEFFICIENT	P VALUE
MetS (≥2 RFs) (n=1973)	68.4±12.3		2.9	.0017	2.9	.0015
No MetS (0 or 1 RF) (n=201)	65.6±11.8	.0017				

B. ACCORDING TO PRESENCE OF NUMBER OF COMPONENTS OF METS		P VALUE FOR TREND	COEFFICIENT AS COMPARED TO 0 OR 1 RF	P VALUE FOR TREND		P VALUE FOR TREND
0 or 1 (n=201)	65.6±11.8	<.001	0 or 1	<.001	–	<.001
2 (n=510)	66.8±12.0		1.3		1.3	
3 (n=751)	68.5±12.4		2.9		2.9	
4 (n=712)	69.5±12.3	<.001	4.0		4.3	

C. ACCORDING TO PRESENCE OF TYPE OF COMPONENTS OF METS	R^2	CHANGE IN R^2	COEFFICIENT FROM REGRESSION MODEL	P VALUE	–	–
Reference model[b]	0.0279				–	–
Waist circumference >100 cm for men and >88 cm for women	0.0413	.0134	3.5	<.0001	–	–
Triglycerides >150 mg/dL	0.0294	.0015	1.16	.03	–	–
HDL cholesterol <40 mg/dL for men and <50 mg/dL for women	0.0279	.0	0.66	.27	–	–
Blood pressure >130/85 mm Hg	0.0275	−.0004	0.48	.53	–	–

Abbreviations: HDL, high-density lipoprotein cholesterol; RF, risk factor; SD, standard deviation. [a]Adjusted for age, sex, race/ethnicity, use of β-blockers, use of calcium channel blockers, exercise, smoking, and prior revascularization. [b]Reference model of heart rate includes age, sex, race/ethnicity, current smoking, and prior revascularization.

Table III. Relationship Between Left Ventricular Ejection Fraction (LVEF) and Heart Rate

A. TOTAL FOR LVEF ANALYSES (N=2117)	HEART RATE, MEAN±SD	P VALUE	UNIVARIATE REGRESSION COEFFICIENT (Y/N)	P VALUE	ADJUSTED[a] REGRESSION COEFFICIENT	P VALUE
LVEF <50% (n=358)	69.7±13.1		1.7	.017	1.8	.009
LVEF ≥50% (n=1785)	68.0±12.2	.017				

B. ACCORDING TO LVEF CATEGORIES		P VALUE FOR TREND	COEFFICIENT AS COMPARED TO LVEF ≥55%	P VALUE FOR TREND		P VALUE FOR TREND
<35% (n=61)	72.1±13.4	.007	4.30	.007	4.5	.004
35%–45% (n=153)	69.5±13.2		1.70		1.8	
45%–55% (n=423)	68.8±12.4		0.99		1.4	
≥55% (n=1457)	67.8±12.2		1.00	–	1	–

Abbreviation: SD, standard deviation. [a]Adjusted for age, sex, race/ethnicity, use of β-blockers, use of calcium channel blockers, exercise, smoking, and prior revascularization.

disease, increased heart rate reflects a degree of left ventricular dysfunction[23] and that an increased rHR could additionally worsen cardiovascular prognosis due to increased shear stress[24] and progression of atherosclerosis.[3]

The limitations of our study include the cross-sectional nature of the analyses; thus, no causation can be established. We did not measure indices for HRV. Although we controlled for exercise in the multiavariable analyses, we did not measure cardio-respiratory fitness in the trial. Patients with MetS were more likely to be receiving β-blockers (74% vs 66%, $P<0.01$). Accordingly, we adjusted the multi-variable model by baseline β-blocker use. However,

this makes our results even more interesting because a lower heart rate is expected with β-blocker use. Since all participants had diabetes and coronary heart disease, our analyses can not be extrapolated to people with MetS but without diabetes or CAD.

In summary, presence of MetS is associated with higher rHR in patients with type 2 diabetes and CAD and may be one way MetS confers additional cardiovascular risk.

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